

Evaluation of Coronary Flow Velocity Dynamics and Flow Reserve in Patients With Kawasaki Disease by Means of a Doppler Guide Wire

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Objectives. To assess the pathophysiologic effects of the coronary sequelae of Kawasaki disease on coronary hemodynamic variables, we regionally evaluated the flow velocity dynamics and flow reserve in coronary vessels with lesions using an intracoronary Doppler flow guide wire.

Background. The pathophysiologic effects of the coronary sequelae of Kawasaki disease on coronary hemodynamic variables have not been completely clarified, and we previously reported some discrepancies between coronary angiographic findings and exercise stress tests in Kawasaki disease.

Methods. Doppler phasic coronary flow velocity was determined using an 0.018-in. (0.046-cm) intracoronary Doppler flow guide wire at rest and during the adenosine triphosphate-induced hyperemic response in 95 patients (75 male, 20 female, mean age 9.8 ± 6.2 years) with Kawasaki disease.

Results. In 25 patients with coronary aneurysms in 29 vessels, the average peak velocity and diastolic to systolic velocity ratio were significantly ($p < 0.05$) decreased in the moderate-sized and large-sized aneurysms. Significantly lower values in coronary flow reserve (CFR) were noted in 3 of 10 vessels with moderate aneurysms and in 4 of 7 vessels with large aneurysms. A signifi-

cant positive correlation ($y = 0.53x + 14.6$, $r^2 = 0.91$) was observed between the percent diameter stenosis evaluated by angiography and that calculated from the flow velocity measurement. However, the percent diameter stenosis calculated from the flow velocity measurement was underestimated compared with that determined by angiography in the stenotic lesions of intermediate severity. A reduced CFR was noted in five of seven vessels with intermediate stenosis ranging from 50% to 75%, and also in three vessels with mild stenosis ranging from 30% to 40%. A reduced CFR was also observed in six of the eight angiographically normal vessels associated with the area of reduced perfusion on exercise thallium-201 myocardial scintigraphy.

Conclusions. Abnormalities in flow dynamics and a reduction in flow reserve were revealed in coronary aneurysms of intermediate to large size and in stenotic lesions, even of mild to intermediate severity, in patients with Kawasaki disease. Abnormalities in the coronary microcirculation, as well as epicardial lesions, contribute to the pathophysiologic responses in Kawasaki disease.

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Kawasaki disease, an acute febrile illness of unknown etiology, is characterized by diffuse vasculitis that affects infants and young children. Its most common and serious clinical feature is the involvement of the coronary arteries, resulting in aneurysmal changes that can lead to stenotic lesions or myocardial ischemia associated with late mortality (1).

The angiographic findings and transformation of the coronary sequelae of Kawasaki disease have been documented by selective coronary angiography (1,2). However, angiography has some disadvantages (3,4) with regard to evaluating the narrowing of the coronary lumen and assessing the physiologic

significance of a variety of dilated or stenotic lesions in the coronary circulation. In addition, we have reported some discrepancies between coronary angiographic findings and exercise stress tests in Kawasaki disease (5,6). The assessment of the physiologic significance of the coronary sequelae of Kawasaki disease should therefore be based not only on the clinical features and angiographic findings, but also on the hemodynamic abnormalities related to the lesions. However, clinical measurements of coronary flow in children have been limited because the relatively large catheters interfered with obtaining the desired measurements. Thus, the pathophysiologic effects of the coronary sequelae of Kawasaki disease on coronary hemodynamic variables have not been completely clarified. This dilemma has now been addressed with a Doppler-tipped angioplasty (0.018 and 0.014 in. [0.046 and 0.035 cm] diameter) guide wire (7-9) developed for the measurement of blood flow velocity. The direct assessment of regional and functional coronary flow dynamics can thus be easily and safely obtained at the time of routine diagnostic angiography, even in children (10). We hypothesized that the flow velocity dynamics and flow reserve would be abnormal in coronary lesions in

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Abbreviations and Acronyms

APV	= average peak velocity
ATP	= adenosine triphosphate
CFR	= coronary flow reserve
DSVR	= diastolic to systolic velocity ratio
ECG	= electrocardiogram
LAD	= left anterior descending coronary artery
LCx	= left circumflex coronary artery
RCA	= right coronary artery
SVR	= stenotic velocity ratio

patients with Kawasaki disease. This method would also permit assessment of the microvascular status.

Methods

Study patients. The study group consisted of 95 consecutive Japanese patients (75 males and 20 females; mean age 9.8 ± 6.2 years, range 1 to 24) who were undergoing routine coronary angiography for the evaluation of coronary sequelae in Kawasaki disease. The interval between the onset of Kawasaki disease and the start of the study was 4 months to 22 years (mean 7.9 ± 5.9). All patients met the clinical criteria for Kawasaki disease and exhibited coronary artery dilation in the acute or healed stage as documented by two-dimensional echocardiography or coronary angiography. None of the patients had received beta-adrenergic blocking agents, calcium channel antagonists or nitrates. All patients received atropine sulfate (0.01 mg/kg body weight) by subcutaneous injection before catheterization. Younger children (<6 years old) received ketamine (1 mg/kg) and diazepam (0.2 mg/kg) as the anesthetic agent. All patients had been free of symptoms during their routine daily activities. The present study was prospectively performed in accordance with the ethical guidelines of the Helsinki Declaration, and according to the rules and regulations for clinical research at our university. The nature of this study was discussed with the patient or parent(s), or both, and written, informed consent for participation was obtained before cardiac catheterization.

Angiographic findings were analyzed visually by three experienced pediatric cardiologists. The 95 patients were classified into four groups, and certain subdivisions were made according to the coronary artery lesions observed on angiography or according to the findings of the exercise stress tests, without interobserver variabilities. All patients exhibited normal left ventricular wall motion as documented by angiography and echocardiography at rest.

Group 1 consisted of 47 patients with Kawasaki disease (mean age 8.6 ± 5.8 years) without angiographic coronary lesions and who had not shown any clinical signs or symptoms of ischemia or positive findings on the exercise electrocardiogram (ECG) or thallium-201 scintigram. None of the patients had clinically significant myocardial damage or carditis in the early stage.

Group 2 consisted of 25 patients (mean age 10.2 ± 6.7 years) with coronary aneurysmal lesions in 29 vessels on angiography. These 25 patients had a single aneurysmal lesion in the unilateral vessel. The 29 lesions were subdivided by size into three groups according to the classification of the Kawasaki Disease Research Committee of the Japanese Ministry of Health and Welfare (11), as follows: small-sized aneurysm (12 lesions in 10 patients, mean age 6.9 ± 5.0 years), moderate-sized aneurysm (10 lesions in 8 patients, mean age 11.4 ± 6.5 years) and large-sized aneurysm (7 lesions in 7 patients, mean age 8.8 ± 8.0 years).

Group 3 consisted of 15 patients (mean age 13.5 ± 5.6 years) who had stenotic lesions in 18 vessels on angiography. These 18 lesions were subdivided into two groups according to the angiographic findings, as follows: localized stenosis (14 lesions) with or without aneurysmal lesion and segmental stenosis (4 lesions) with or without intercoronary collateral circulation. The severity of the stenotic lesions was determined as percent diameter relative to the angiographically normal adjacent reference segment using digital computer-assisted calipers (Digitizer KD 4300, Graphtec Co., Tokyo, Japan).

Group 4 consisted of eight patients with Kawasaki disease (mean age 12.6 ± 3.5 years) with ischemic findings on the exercise stress tests but with no significant angiographic lesions. These patients had not shown any symptoms of myocardial ischemia.

Coronary flow velocity measurements. After diagnostic coronary angiography and left ventriculography, coronary flow velocity was measured using a 175-cm long, 0.018-in. diameter, flexible, steerable angioplastic guide wire with a 12-MHz piezoelectric ultrasound transducer integrated into its tip (FloWire, Cardiometrics, Inc.). The measurement of coronary flow velocity with the Doppler guide wire has been described in detail by Doucette et al. (7), Segal et al. (8) and Ofili et al. (9). As we previously reported (10), after completion of angiography, the Doppler guide wire was advanced through a 5F guiding Judkins-type coronary catheter into each target coronary artery. The catheter position was adjusted to obtain a maximal and intense spectral flow velocity signal within the vessel. The Doppler guide wire was coupled to a real-time spectrum analyzer, videocassette recorder and video image printer. Arterial pressure signals obtained with the guiding catheter and the ECG were also monitored continuously, with input to the video display.

The average peak velocity (APV) and the diastolic to systolic velocity ratio (DSVR) were obtained from the left anterior descending coronary artery (LAD, segment 7), left circumflex coronary artery (LCx, segment 13) and right coronary artery (RCA, segment 3) in groups 1 and 4. In groups 2 and 3, baseline flow velocity data were obtained at least 1 cm proximal and distal to the lesion, taking care to avoid placing the catheter in any small side branch. Then the same variables were obtained from the middle of the aneurysm in group 2 and just at the stenotic lesion in group 3. The APV represents the average of the instantaneous peak velocity in centimeters per second and has been used as an indicator of flow volume when

Table 1. Age-Related Coronary Flow Reserve in 47 Patients With Kawasaki Disease and Normal Coronary Arteries (group 1)

Age Group (yr)	No. of Pts	Coronary Flow Reserve		
		LAD	LCx	RCA
1-5 (2.81 ± 1.60)	16	2.07 ± 0.30	1.80 ± 0.23*	2.47 ± 0.25
6-15 (9.23 ± 2.98)	22	2.69 ± 0.40†	2.30 ± 0.38†‡	2.64 ± 0.42
16-23 (17.78 ± 2.54)	9	3.50 ± 0.45§	3.21 ± 0.42§	3.56 ± 0.40§

*p < 0.001 versus RCA. †p < 0.001 versus age group 1 to 5 years. ‡p < 0.05 versus LAD. §p < 0.001 versus age groups 1 to 5 years and 6 to 15 years. Data are presented as range (mean ± SD) for age groups and mean value ± SD for coronary flow reserve. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; Pts = patients; RCA = right coronary artery.

the cross-sectional area of the vessel was unchanged. The DSVR provides an indicator of the pulsatility of the flow. The coronary artery segment number indicates the area of the coronary arteries according to the system reported by the American Heart Association (12).

After the baseline distal arterial flow velocity data were obtained at the each target position, a bolus injection of adenosine triphosphate (ATP, 1.0 µg/kg) was administered through the guiding catheter into each coronary artery. Data were recorded continuously throughout peak hyperemia. As previously reported (10,13,14), the intracoronary administration of ATP exhibits vasodilator potency in the microvascular bed without significantly dilating the epicardial coronary vessels and without significantly changing heart rate and blood pressure. The dose of intracoronary ATP used in this study (1 µg/kg) was based on our preliminary study (14). Hyperemic flow velocity data were obtained distal to the lesion in groups 2 and 3. In patients who had recanalization (segmental stenosis) after occlusion in the RCA through which the guiding wire could not be passed, we evaluated the hyperemic response in the collateral vessel from the LCx to the posterior descending branch (segment 4) distal to the segmental stenosis in the RCA. The coronary flow reserve (CFR) was assessed by calculating the quotient of the peak hyperemic APV after intracoronary infusion of ATP and the baseline APV distal to the lesions.

Because there are some significant differences in the coronary hemodynamic variables among the age groups and the vessels in childhood, as we reported elsewhere (10,15), the coronary hemodynamic data from group 1 were categorized by age as follows: 1 to 5 years (mean age 2.81 ± 1.60 years, n = 16), 6 to 15 years (mean age 9.23 ± 2.98 years, n = 22) and 16 to 23 years (mean age 17.78 ± 2.54 years, n = 9). The CFR in each vessel with aneurysmal or stenotic lesions was compared with the reference value in group 1 with regard to patient's age group and the vessel affected.

The severity of the stenosis (stenotic velocity ratio [SVR]) in the flow velocity measurement was assessed by calculating the quotient of APV obtained just at the lesion and that proximal to the lesion, expressed as the SVR (SVR = APV just at the lesion/APV proximal to the lesion). The percent diameter of the stenosis in the flow velocity measurement was calculated as $(1 - 1/\sqrt{\text{SVR}}) \times 100$ (16). The correlation

between the percent diameter of the stenosis measured with coronary angiography and that calculated from the flow velocity measurement was evaluated using simple linear regression analysis in 14 vessels with localized stenosis.

Statistical analysis. Data are expressed as the mean value ± SD, unless otherwise indicated. Analysis of the significance of the differences in Doppler flow velocity variables among three vessels in group 1 and angiographic subgroups (small, moderate and large aneurysms) in group 2 was done using analysis of variance with the Bonferroni multiple comparison test. Comparison of data obtained at the middle portion of the lesion, as well as proximal and distal to the lesion in group 2, were also performed using the same test. Differences in CFR in groups 2, 3 and 4 were considered statistically significant when they were <2 SD of the mean values in group 1. The level p < 0.05 was statistically significant.

Results

Coronary flow reserve in angiographically normal coronary arteries. A significant age-related increase in the CFR was observed in all three coronary vessels in patients in group 1 (Table 1). The CFRs in the LCx were significantly lower than those in the RCA in the age group 1 to 5 years and those in the LAD in the age group 6 to 15 years.

Coronary flow velocity dynamics in patients with aneurysmal lesions. There were no significant differences among small, moderate and large aneurysms with regard to values for APV and DSVR proximal to the lesion at rest (Table 2). The APV and DSVR values did not change significantly at the middle site in small aneurysms, but were significantly decreased at the middle site in aneurysms of moderate (APV: 20.1 ± 2.9 to 12.8 ± 5.2; DSVR: 2.6 ± 0.6 to 1.7 ± 0.4) or large size (APV: 21.6 ± 4.1 to 9.4 ± 0.8; DSVR: 2.5 ± 0.5 to 1.3 ± 0.2). The ratios of APV and DSVR at midlesion to the proximal portion of the lesion significantly decreased according to the size of the aneurysmal lesion, being significantly lower (p < 0.001) in aneurysms of moderate and large size than those of small size (Table 2). The APV and DSVR values did not differ in portions that were proximal or distal to the lesion in vessels with aneurysms of moderate or large size.

In assessing the CFR in each vessel with aneurysmal lesions,

Table 2. Coronary Flow Velocity Change in Coronary Aneurysms at Rest and Coronary Flow Reserve in 25 Patients With Kawasaki Disease and Aneurysmal Lesions in 29 Coronary Vessels (group 2)

Size of Aneurysm	No. of Vessels	APV (cm/s)			DSVR			APV Ratio*	DSVR Ratio†	Reduced CFR
		Proximal	Midlesion	Distal	Proximal	Midlesion	Distal			
Small	12	23.8 ± 4.4	22.8 ± 3.5	23.9 ± 3.6	2.8 ± 0.6	2.7 ± 0.6	3.0 ± 0.6	0.96 ± 0.05	1.00 ± 0.10	0/12 (0%)
Moderate	10	20.1 ± 2.9	12.8 ± 5.2‡§	19.9 ± 4.6	2.6 ± 0.6	1.7 ± 0.4	2.6 ± 0.5	0.64 ± 0.19¶	0.67 ± 0.14¶	3/10 (30%)
Large	7	21.6 ± 4.1	9.4 ± 0.8‡§	23.0 ± 4.5	2.5 ± 0.5	1.3 ± 0.2	2.6 ± 0.5	0.44 ± 0.14¶	0.49 ± 0.03¶	4/7 (57%)

*Ratio of average peak velocity at the midlesion to that proximal to the aneurysmal lesion. †Ratio of diastolic to systolic velocity ratio at the midlesion to that proximal to the aneurysmal lesion. ‡p < 0.01 versus distal segment. §p < 0.05 versus proximal segment. ||p < 0.05 versus proximal and distal segments. ¶p < 0.001 versus small-sized aneurysm. APV = average peak velocity; CFR = coronary flow reserve; DSVR = diastolic to systolic velocity ratio.

the vessels with small aneurysms exhibited no significant abnormality in CFR values. However, significantly lower CFR values were noted in three of 10 vessels with aneurysms of moderate size and in four of seven vessels with aneurysms of large size.

Coronary flow velocity dynamics in patients with stenotic lesions. The flow velocity was significantly accelerated at the stenotic lesion. In the 14 vessels with localized stenosis in the 11 patients in group 3, the percent diameter stenosis measured by coronary angiography was $40.9 \pm 18.6\%$, and that calculated by flow velocity dynamics was $36.4 \pm 10.7\%$ (Table 3). A significant positive correlation ($y = 0.53x + 14.6$, $r^2 = 0.91$) was observed between the percent diameter stenosis evaluated by coronary angiography and that calculated from the flow

velocity measurement (Fig. 1). However, the percent diameter stenosis calculated by flow velocity measurement was relatively less than that determined by coronary angiography in the intermediate to severe stenotic lesions.

A significant reduction in CFR was noted in 8 of the 14 vessels that exhibited localized stenosis ranging in severity from 20% to 75% on coronary angiography. The reduction in CFR was noted in five of seven vessels with intermediate stenosis ranging in severity from 50% to 75%, and also in three vessels with mild stenosis ranging from 30% to 40%. A reduced CFR was also observed in all eight patients with stenotic lesions and ischemic findings on the stress test. In addition, six of eight vessels with a reduced CFR exhibited a second aneurysm of moderate or large size. However, a normal CFR

Table 3. Coronary Flow Velocity Dynamics in 15 Patients With Kawasaki Disease and Stenotic Lesions in 18 Vessels (group 3)

Pt No./ Gender	Age (yr)	Coronary Angiography				Ischemic Findings on Stress Test		Flow Velocity Dynamics			
		Lesion	%Stenosis	Secondary Lesion	Collateral Vessel	Treadmill	Ex. TI-Scint.	SVR	%Stenosis	CFR	Reduced CFR
1/M	5	LS in LAD	25	—		Normal	Normal	1.9	28	1.82	WNL
2/F	8	LS in RCA	25	ANm		Normal	Normal	2.0	30	2.02	WNL
3/M	10	LS in LAD	60	ANm		Normal	Ant(+)	3.3	45	1.62	Reduced
4/M	11	LS in LAD	20	—		Normal	Ant(+)	1.5	19	4.32	WNL
		LS in RCA	75	ANm			Inf(+)	4.0	52	1.72	Reduced
5/M	11	LS in LAD	25	ANs		Leads II, III and aVF	Ant(+)	1.8	27	2.41	WNL
		LS in RCA	50	ANm			Inf(+)	3.7	48	1.83	Reduced
6/M	11	LS in RCA	70	ANm		Normal	Normal	3.9	50	2.22	WNL
7/M	13	LS in LAD	30	—		Normal	Ant-Sept(+)	2.3	34	1.83	Reduced
8/F	16	LS in RCA	70	ANm		Normal	Inf(+)	4.0	52	1.81	Reduced
9/M	17	LS in LAD	40	ANm		Leads II, III and aVF	Ant-Lat(+)	2.2	33	1.83	Reduced
		LS in RCA	50	—				3.3	45	3.62	WNL
10/M	17	LS in RCA	40	ANm		Normal	Inf(+)	2.4	35	1.33	Reduced
11/M	18	LS in RCA	65	—		Normal	Inf(+)	3.7	48	1.91	Reduced
12/M	14	SS in RCA	ND		LCx→4PDB	Leads II, III and aVF	Inf(+)	—	NC	CV:1.71	Reduced
13/M	20	SS in RCA	ND		LCx→4PDB	Normal	Inf(+)	—	NC	CV:2.02	Reduced
14/M	20	SS in LAD	ND		—	Normal	Normal	0.76	0	3.82	WNL
15/M	24	SS in LAD	ND		—	Normal	Ant-Lat(+)	0.71	0	2.88	WNL

(+) or (−) = presence or absence of redistribution of thallium-201; ANm = moderate-sized aneurysm; ANs = small-sized aneurysm; Ant = anterior; CFR = coronary flow reserve; CV = collateral vessel; Ex. TI-Scint. = exercise loading thallium-201 myocardial scintigraphy; F = female; Inf = inferior; Lat = lateral; LS = localized stenosis; M = male; NC = not calculated; ND = not determined; Sept = septal; SS = segmental stenosis; SVR = stenotic velocity ratio; WNL = within normal limits; 4PDB = posterior descending branch of right coronary artery; other abbreviations as in Table 1.

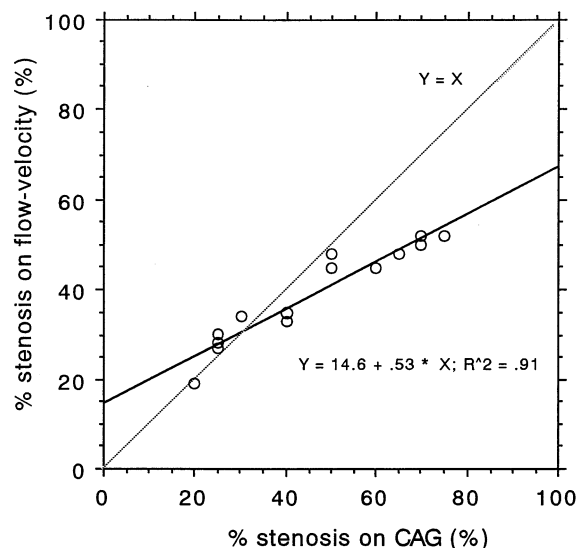


Figure 1. Correlation between percent diameter stenosis evaluated by coronary angiography (CAG) and that calculated by flow velocity measurements. A statistically significant positive correlation ($y = 0.53x + 14.6$, $r^2 = 0.91$) was observed between the values for percent diameter stenosis evaluated by coronary angiography and that calculated by flow velocity measurements. However, the percent diameter stenosis calculated by flow velocity measurements was relatively less than that determined by coronary angiography in the stenotic lesions of intermediate to severe severity.

was noted even in the vessels with 50% or 70% stenosis complicated by an aneurysm of moderate size. A reduction in CFR was noted in the vessel with 65% stenosis but without a second aneurysm.

Two of the four vessels with segmental stenosis had angiographically well developed recanalized vessels at the lesion. The other two vessels with poorly developed recanalization exhibited well developed intercoronary collateral circulation from the LCx to the distal portion of the RCA. In these four vessels with segmental stenosis, a normal CFR was noted in the two vessels with well developed recanalization at the lesion, although the CFR was reduced in the other two vessels with

poorly developed recanalization and intercoronary collateral circulation.

Coronary flow velocity dynamics in patients with ischemic findings on stress tests but normal angiographic results. In the eight patients with ischemic findings on the exercise stress test but no abnormalities on coronary angiography, no abnormalities in APV and DSVR were noted through the distal to proximal portion in each vessel. The values for the CFR in each vessel are shown in Table 4. A reduction in CFR was noted in six of the eight vessels associated with the area of reduced perfusion on exercise thallium-201 myocardial scintigraphy.

Discussion

The major findings of the present study are as follows: 1) the APV and DSVR were significantly decreased in the aneurysms of moderate or large size; 2) significantly lower CFR values were noted in the vessels with aneurysms of moderate or large size; 3) although there was some correlation between the incidence of the reduction in CFR and the severity of the percent diameter stenosis, a reduction in CFR was noted even in vessels with mild stenosis ranging in severity from 30% to 40%; and 4) a reduction in CFR was noted in six of the eight vessels associated with the area of reduced perfusion on the exercise thallium-201 myocardial scintigram in patients without coronary lesions on angiography. Although a significant reduction in CFR was correlated with the size of the aneurysm or the severity of stenosis, there was heterogeneity in the effects of the coronary lesions on CFR.

Coronary flow velocity profile at rest. In aneurysmal lesions, a significant decrease in APV and DSVR was observed in lesions of moderate or large size and was significantly correlated with the size of the lesion. However, even in moderate- and large-sized lesions, the APV and DSVR distal to the aneurysm exhibited the same values as those recorded proximal to the lesion. These findings showed that the coronary aneurysms in patients with Kawasaki disease significantly reduced the velocity and pulsatility of coronary blood flow

Table 4. Coronary Flow Velocity Dynamics in Eight Patients With Kawasaki Disease and Ischemic Findings on Exercise Stress Testing and Normal Coronary Arteries on Angiography (group 4)

Pt No./Gender	Age (yr)	Ischemic Findings on Stress Test					Coronary Flow Reserve			Reduced CFR
		Treadmill	Ex. TI-Scint.	LVG	CA	Velocity Pattern	LAD	LCx	RCA	
1/M	12	Leads II, III and aVF	Ant(+)	Normal	Normal	Normal	1.8	1.62	2.56	LAD, LCx
2/M	7	Normal	Ant-Lat(+)	Normal	Normal	Normal	1.62	2.02	2.33	LAD
3/F	9	Normal	Ant(+) Inf(+)	Normal	Normal	Normal	1.71	2.01	1.82	LAD, RCA
4/M	17	Normal	Ant(+)	Normal	Normal	Normal	2.22	3.05	3.43	LAD
5/M	13	Normal	Ant-Sept(-)	Normal	Normal	Normal	1.8	2.32	3.12	LAD
6/M	12	Normal	Ant-Sept(+)	Normal	Normal	Normal	3.33	3.04	3.3	WNL
7/M	17	Normal	Ant(+)	Normal	Normal	Normal	2.21	3.23	3.62	LAD
8/M	14	Normal	Ant(+)	Normal	Normal	Normal	3.08	3.02	4.33	WNL

CA = coronary angiography; LVG = left ventriculography; other abbreviations as in Tables 1 and 3.

within the lesion, but had no significant effect on the flow velocity pattern distal to these lesions, at least at rest. These significant reductions in flow velocity and pulsatility in the aneurysmal lesions may have caused a variation in shear stress, flow turbulence and particle (e.g., platelet) resistance time. These variables may be particularly relevant to atherosclerotic plaque development or arterial thrombosis, resulting in the development of stenotic lesions.

In stenotic lesions, we observed a significant positive correlation between the percent diameter stenosis measured by coronary angiography and that calculated from flow velocity measurements. However, in the stenotic lesions of intermediate severity, the percent diameter stenosis assessed by flow velocity measurements was underestimated compared with that determined by coronary angiography. The percent diameter stenosis assessed by coronary angiography is one of several factors that can influence flow resistance and the pressure gradient across a given stenosis. The length of the lesion, the viscosity of blood and the characteristics of laminar flow that influence flow velocity all contribute to the effects of obstructive narrowing on hemodynamic variables. We considered that the lower percent diameter stenosis obtained by flow velocity measurements may be the result of these numerous factors.

Coronary flow reserve after ATP loading. A significant reduction in CFR was noted in the coronary vessels with aneurysms of moderate or large size and was also correlated with the size of the aneurysmal lesion. This finding showed that an aneurysmal lesion with a reduction in values for APV and DSVR would lead to compensatory dilation of the arterioles to maintain the basal coronary blood flow distal to the lesion, resulting in a reduction in CFR. This is because the intracoronary infusion of ATP exhibits vasodilator potency in the microvascular bed but does not significantly dilate the epicardial coronary vessels (10,14).

A significant reduction in CFR was noted in 8 of the 14 vessels with stenotic lesions ranging from 20% to 75% in diameter stenosis as determined by coronary angiography, and even in the three vessels with stenotic lesions of mild severity (30% to 40%) on coronary angiography. This reduction in CFR in the mild or intermediate stenotic lesions was more common than what we had recognized clinically. However, it has been reported (3,17,18) that the angiographic appearance of coronary stenosis does not always indicate its physiologic significance, particularly in stenotic lesions of intermediate severity (50% to 70% diameter stenosis). Gould et al. (19), who conducted an experimental study in dogs, reported that the rest mean flow was not affected until 85% constriction occurred, whereas the hyperemic response was blunted even when there was 35% to 45% narrowing and decreased precipitously before rest flow was affected. The findings in the present study also indicate that, although very mild or very severe stenoses exhibited the expected results, it is difficult to evaluate clinical significance or to determine the indications for treating stenotic lesions of mild to intermediate severity only by angiographic findings (3,18,20). Therefore, patients

with Kawasaki disease with stenotic lesions on angiography, particularly those of mild to intermediate severity, should be evaluated with respect to flow dynamics and CFR.

A reduced CFR was also observed in six of the eight angiographically normal vessels that showed some ischemic findings on exercise stress testing. This suggests that such patients with Kawasaki disease have a reduced dilatory potency of the small coronary artery that is not visualized on coronary angiography. Although the precise mechanism leading to impairment of coronary vasodilation in patients with Kawasaki disease has not been clarified, we have reported (21) that patients with Kawasaki disease with a reduced CFR but no stenotic lesions on angiography exhibited microvascular lesions (microangiopathies) in electron microscopic studies of myocardial biopsy specimens, as reported in diabetes, hypertension or cardiomyopathy (22,23). Such microvascular abnormalities may play a primary or secondary role in reducing the CFR in patients with Kawasaki disease, which could lead to myocardial ischemia in some instances. The reduction of CFR in the vessels with mild stenosis may be associated with the microvascular abnormalities, too.

Two vessels with well developed recanalization after occlusion did not exhibit a stenotic flow pattern or reduced CFR, whereas a significant reduction in CFR was detected in two vessels with the poorly developed recanalization and well developed collateral circulation from the LCx to the four posterior descending branches of the RCA. In the pediatric population, the formation of collateral vessels is not seen on angiography unless total or near-total occlusion is present (24-26) and appears to require more severe stenotic lesions than those in adults. However, the functional importance of coronary collateral vessels in children is still a subject of debate (24,26-29), and there have been few studies on the flow reserve in collateral circulation. The findings of the present study showed that a normal CFR would be maintained in a vessel with well developed recanalization but would not be completely maintained only by the collateral circulation.

Clinical implications. The present study demonstrated that the abnormal flow velocity profile and the reduced CFR occurred in the coronary vessels with aneurysmal or stenotic lesions, even of mild to intermediate severity. It was also revealed that some of the patients with Kawasaki disease had a microvascular dysfunction not detected by coronary angiography. This study explained the discrepancy in the findings between angiographic findings and stress tests and clarified that the evaluation of the pathologic significance of coronary artery lesions in Kawasaki disease should be based on the functional and regional analysis of flow velocity dynamics as well as on angiographic findings. The functional assessment of the coronary flow dynamics, including the flow reserve, is also important and useful in understanding the pathophysiology of the coronary lesions and in determining the effective therapy for preventing an ischemic attack or sudden death in patients with Kawasaki disease.

Study limitations. Although the Doppler flow guide wire provides a convenient method of obtaining phasic flow velocity

data in the coronary arteries, such intracoronary Doppler catheter techniques have some limitations, as previously described in detail (30–32). Optimal placement of the transducer approximately parallel to blood flow is required for the accurate detection of peak velocity, because this is a Doppler-based technique. We always directed the distal tip of the Doppler guide wire to identify the maximal, most intense, spectral flow velocity signal. Relatively stable placement of the Doppler guide wire was consistently done in all patients. Signals of satisfactory flow velocity were obtained without repositioning or manipulating the guide wire, even during the injection of ATP. In the presence of stenotic lesions, flow acceleration is present in the convergence zone before the stenoses and within the lesion. We attempted to avoid this region of flow acceleration by sampling at a position that was >1.0 cm proximal to the stenotic lesion. Flow velocity profiles and CFR values were reproducible in the repeated measurements in all patients.

Measurements of coronary flow velocity and flow reserve were obtained with the guiding catheter positioned in the coronary ostium. Obstruction by the guiding catheter at the coronary artery ostium, which interfered with coronary flow, was minimized by the use of a 5F guiding catheter. As previously reported (11), coronary sinus blood flow measured with the continuous thermodilution method was unchanged before and after the insertion of a 5F catheter into the left coronary artery ostium. In addition, for flow-velocity, the small cross-sectional area of the Doppler guide wire (0.16 mm^2) inserted into the coronary artery is $\sim 5\%$ of the cross-sectional area (3.14 mm^2) of a vessel whose diameter is 2.0 mm, and is $\sim 20\%$ of the residual cross-sectional area (0.79 mm^2) of a vessel whose diameter is 2.0 mm with 50% diameter stenosis. Although a stenotic error produced by the additional cross-sectional area of the Doppler guide wire may, in theory, overestimate the translesional hemodynamic findings in severe stenotic lesion, the percent diameter stenosis calculated by flow velocity measurements was found to be underestimated compared with that observed by coronary angiography. We therefore consider that the Doppler guide wire did not interfere with coronary flow at the site of stenosis.

Conclusions. The present study showed that flow dynamics were abnormal and flow reserve was reduced in the coronary aneurysms and stenotic lesions of even mild to intermediate severity in patients with Kawasaki disease. Although a significant reduction in CFR was correlated with the aneurysmal size or stenotic severity, there was also heterogeneity in the effects of the coronary lesions on CFR. Evaluation of the pathologic significance of coronary artery lesions in Kawasaki disease should therefore be based on the functional and regional analysis of flow velocity dynamics as well as on angiographic findings. In addition, in assessing the pathophysiology or long-term prognosis of the coronary sequelae in patients with Kawasaki disease, it is necessary to take into consideration the abnormalities in the coronary microcirculation, as well as the epicardial lesions.

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References

1. Kato H, Ichinose E, Yoshioka F, Takeuchi T, Matsunaga T, Suzuki K. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. *Am J Cardiol* 1982;49:1758–66.
2. Nakano H, Ueda K, Saito A. Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease. *Am J Cardiol* 1985;56:846–51.
3. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary angiogram predict the physiologic importance of a coronary stenosis? *N Eng J Med* 1984;310:819–24.
4. Kusemaul WG III, Popp RL, Narcini J. Accuracy and reproducibility of visual coronary stenosis estimates using information from multiple observers. *Clin Cardiol* 1992;15:154–62.
5. Hamaoka K, Ohmochi Y, Onouchi Z. Coronary flow reserve in children with Kawasaki disease without angiographic evidence of coronary stenosis. *Am J Cardiol* 1992;69:691–2.
6. Ohmochi Y, Onouchi Z, Oda Y, Hamaoka K. Assessment of effects of intravenous dipyridamole on regional myocardial perfusion in children with Kawasaki disease without angiographic evidence of coronary stenosis using positron emission tomography and H_2^{15}O . *Coron Artery Dis* 1995;6:555–9.
7. Doucette JW, Corl PO, Payne HM, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992;85:1895–1911.
8. Segal J, Kern MJ, Scott NA, et al. Alterations of phasic coronary artery flow velocity in humans during percutaneous coronary angioplasty. *J Am Coll Cardiol* 1992;20:276–86.
9. Ofili EO, Labovitz AJ, Kern MJ. Coronary flow velocity dynamics in normal and diseased artery. *Am J Cardiol* 1993;71:3D–9D.
10. Hamaoka K, Onouchi Z, Ohmochi Y, Sakata K. Coronary arterial flow-velocity dynamics in children with angiographically normal coronary arteries. *Circulation* 1995;92:2457–62.
11. Kawasaki Disease Research Committee of Japanese Ministry of Health and Welfare. Diagnostic criteria of the cardiac involvement in Kawasaki disease. Tokyo, Japan: Ministry of Health and Welfare, 1983.
12. American Heart Association Committee Report. A reporting system on patients evaluated for coronary artery disease. *Circulation* 1975;51:5.
13. Yamada H, Azuma A, Hirasaki S, et al. Intracoronary adenosine 5'-triphosphate as an alternative to papaverine for measuring coronary flow reserve. *Am J Cardiol* 1994;74:940–1.
14. Hamaoka K, Onouchi Z. Effects of intracoronary adenosine triphosphate on coronary flow velocity dynamics in children. *Jpn Heart J* 1997;38:39–52.
15. Hamaoka K, Onouchi Z, Kamiya Y. Coronary sinus blood flow and coronary haemodynamic function in children: measurement by the continuous thermodilution method with coronary sinus cannulation via the femoral vein. *Br Heart J* 1991;65:171–3.
16. Kern MJ, Aguin FV, Bach RG, Carciolo EA, Donohue TJ, Labovitz AJ. Fundamentals of translesional pressure-flow velocity measurement: part II. *Cathet Cardiovasc Diagn* 1994;31:137–43.
17. Wilson RF, Laxson DD. A clinician's guide to assessing the physiologic significance of arterial stenoses. *Cathet Cardiovasc Diagn* 1993;29:93–8.
18. Harrison DG, White CW, Hiratzka LF, et al. The values of lesion cross-sectional area determined by quantitative angiography in assessing the significance of proximal left anterior descending coronary arterial stenosis. *Circulation* 1984;69:1111–9.
19. Gould KL, Lipscom K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 1974;33:87–94.
20. Kern MJ, Donohue TJ, Aguirre FV, et al. Assessment of angiographically intermediate coronary artery stenosis using the Doppler flowire. *Am J Cardiol* 1993;71:26D–33D.
21. Liu AM, Hamaoka K, Onouchi Z, Aihara K. Studies on the myocardial

- microvasculature and interstitium in Kawasaki disease [in Japanese]. *Prog Med* 1997;17:2165.
22. Cannon RO, Watson RM, Rosing DR, Epstein SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1983;1:1359-73.
 23. Houghton TL, Frank MJ, Carr AA, VonDohlen TW, Prisant M. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. *J Am Coll Cardiol* 1990;15:43-51.
 24. Tatara K, Kusakawa S, Itoh K, et al. Collateral circulation in Kawasaki disease with coronary occlusion or severe stenosis. *Am Heart J* 1991;121:797-802.
 25. Hamaoka K, Onouchi Z, Ohmochi Y. Coronary collateral development in Kawasaki disease. In: Takahashi M, Taubert K, editors. *Proceedings of the 4th International Symposium on Kawasaki Disease*. American Heart Association: Dallas (TX) 1993:391-5.
 26. Onouchi Z, Hamaoka K, Kamiya Y, et al. Transformation of coronary aneurysm to obstructive lesions and the role of collateral vessels in myocardial perfusion in patients with Kawasaki disease. *J Am Coll Cardiol* 1993;21:158-62.
 27. Hamaoka K, Ohmochi Y, Onouchi Z. Reversible left ventricular dysfunction with coronary stenotic or obstructive lesions in Kawasaki disease. *Coron Artery Dis* 1993;4:83-6.
 28. Hansen JF. Coronary collateral circulation: clinical significance and influence on survival in patients with coronary artery occlusion. *Am Heart J* 1989;117:290-5.
 29. Helfant RH, Vokoras PS, Golin R. Functional importance of the human coronary collateral circulation. *N Engl J Med* 1971;284:1277-81.
 30. Wilson RF, Langhain DE, Ackell PH. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. *Circulation* 1985;72:82-92.
 31. Marcus ML, Wilson RF, White CW. Methods of measurement of myocardial blood flow in patients: a critical review. *Circulation* 1987;76:245-53.
 32. McGinn AL, White CW, Wilson RF. Interstudy variability in coronary flow reserve: the importance of heart rate, arterial pressure and ventricular preload. *Circulation* 1990;81:1319-30.